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EXAMINER	
KERR, KATHLEEN M	
ART UNIT	PAPER NUMBER
1652	20

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Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/478,598	RAO ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-118* is/are pending in the application.

4a) Of the above claim(s) *84-96 and 108-114* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-83,97-107 and 115-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 September 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office actions, a Final rejection (Paper No. 10, mailed on January 2, 2002) and an Advisory action (Paper No. 13, mailed on May 8, 2002), Applicants filed an amendment (Paper No. 11 filed on April 9, 2002) an RCE received on September 3, 2002 (Paper No. 17), and a supplemental amendment (Paper No. 18 received on September 3, 2002). Both Paper No. 11 and Paper No. 18 have been entered. Paper No. 11 amended Claims 88 and 109.

Claims 54-118 are pending in the instant Office action. Claims 84-96 and 108-114 are withdrawn from consideration, as noted previously, as non-elected inventions. Thus, Claims 54-83, 97-107, and 115-118 will be examined herein.

Priority

2. The instant application is granted the benefit of priority for the U.S. non-Provisional Application No. 08/988,015 filed on December 10, 1997 as requested in the transmittal and the first lines of the specification.

Information Disclosure Statement

3. As previously noted, an information disclosure statement was filed on January 6, 2000 (Paper No. 2), the references of which have been considered.

Drawings

4. The drawings filed on April 9, 2002 (with Paper No. 11) are not a complete set of drawings and cannot be considered by the Draftsman. Figure 4 has been omitted. In the transmittal sheet, 10 sheets of drawings are cited as being filed while only 8 sheets (note "8/8" on the last page of the drawings) have been filed. New formal drawings affecting changes requested by the Draftsman in the PTO-Form-948 attached to Paper No. 10 are required. Appropriate correction is required in response to the instant Office action and may not be held in abeyance (see 37 C.F.R. § 1.85(a)).

Sequence Compliance

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a) In Figure 1, seven amino acid sequences are disclosed without benefit of SEQ ID NOs.

b) In Figure 2, one amino acid sequence is disclosed without benefit of a SEQ ID NO.

c) In Figure 4, one DNA sequence is disclosed without benefit of a SEQ ID NO.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the

same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Objections to the Specification

6. The drawings are objected to for having inappropriate labels. Figures 1 and 1A should be Figures 1A and 1B. Appropriate correction to the drawings and the brief description of the drawings on page 3 of the instant specification is required.

7. The specification is objected to for being confusing with respect to the sequence listing. The sequence listing filed on September 3, 2002 contains eleven sequences. No SEQ ID NOs are mentioned in the specification. It is unclear why said sequences are in the sequence listing if they are not described in the specification. All SEQ ID NOs in the sequence listing must be described in the specification. Appropriate correction is required.

8. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the source species, *Glycine max,* of the example VSP protein for completeness.

9. The specification is objected to for the following typographical errors in the specification:

a) On page 3, the abbreviation "VSP" is used without definition upon its first appearance in the specification.

b) On page 8, line 14, the following is a typographical error "5□–3□".

c) On page 18, line 4, Figure 1 is described as having "blue" color, but the figures are in black and white.

d) On page 21, line 8, the following is a typographical error "37□C".

e) On page 21, line 11, the following is a typographical error "30□C".

Appropriate correction for each error is required.

Claim Objections

10. The following claims are objected to for the noted typographical errors:

a) Claim 60, as filed on November 9, 2000 as a new claim, contains "[involve]" which must be deleted.

b) In Claim 62, the phrase "determined by" should be ---determined using--- to appropriately describe the claimed subject matter.

c) Claim 117 has inappropriate punctuation in the Markush group; appropriate punctuation requires a comma after "analysis" and a comma and ---and--- after "prediction".

Appropriate correction is required.

11. Claims 59, 74, and 99 are objected to under 37 C.F.R. § 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In each case, the claims attempt to limit the term "essential amino acids". However, in the specification on page 5, the amino acids listed in

Claims 59, 74, and 99 are defined as the essential amino acids. Thus, the instant claims cannot further limit the subject matter of their parent claims as interpreted in light of the specification.

12. Claims 70, 115, and 116 are objected to under 37 C.F.R. § 1.75 as being substantial duplicates of Claims 58, 69, and 71, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See M.P.E.P. § 706.03(k).

Claim 69 is equivalent to Claim 58 except for two things: (1) Claim 69 requires the engineered protein to have increased nutritional value while Claim 58 requires an increase in levels of nutritionally essential amino acids and (2) Claim 58 requires "interacting molecules" while Claim 69 requires antibodies. Number 1 is the same limitation in light of the specification. Number 2 is made equivalent in Claim 70 whose further limitation is that the interacting molecules be antibodies.

For Claims 115 and 116 matching Claims 69 and 71, respectively, the argument for Number 1 above is reiterated.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 54-68, 117, and 118 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. The phrase "whose conformation is unavailable" is unclear. In the art, the term "conformation" typically refers to one of many three-dimensional structures that a particular polypeptide can adopt, such as open (so as to accept substrates) vs. closed, transition state conformations, etc. However, other than folded vs. unfolded, little discussion of conformation is identified in the specification. The ability of a conformation to be "available" is confusing. The claims imply that the three-dimensional structure of the polypeptide to be altered is unknown so that only rudimentary forms of structure determination, such as antibody binding, can be used by the skilled artisan. However, this interpretation is merely a guess on the part of the Examiner. Clarification is required.

14. Claims 57 and 72 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "dimerizing proteins" is unclear as to its metes and bounds. No definition is found in the specification; the term in the art is indicative of identical proteins oligomerizing. It is unclear if the use of the term herein is defined as the interacting molecules being proteins that specifically interact with one additional protein to form a dimer (oligomer of two) or if other multimers or even mixed dimmers are also encompassed.

The Examiner notes that this rejection was previously set forth in Paper No. 8. Applicants argued that working examples were provided using dimerizing proteins in the detection of conformational changes on pages 14 and 21. On neither page does the term "dimerizing" appear to the Examiner's knowledge. A specific citation is required. Moreover, any such examples do not define the metes and bounds of the term as noted above. Applicants also argued that dimerizing proteins are well-known in the art. Clearly, the Examiner agrees

with this position as noted above; however, the metes and bounds are unclear based on this interpretation in the art concerning dimmers vs. multimers in the art. Appropriate clarification is required.

15. Claims 65, 80, and 105 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "correctly folded variants" is unclear as to its metes and bounds. Must the protein fold be exactly the same? If enzymatic activity remains, is the folded variant sufficiently "correct"? In the claims, the folding is assayed by antibody recognition; however, antibodies recognize specific parts of a protein and not the entire protein. Thus, where one antibody might recognize a variant, wherein said variant is considered to be "correctly folded", another antibody to a different portion of the protein might not recognize this same variant, wherein said variant would be considered to not be "correctly folded". Is a set of antibodies required? If so, how many must be included in the set to ensure, statistically, that all facets of the folded conformation as being monitored by the antibody binding? Appropriate clarification is required.

16. Claims 66, 67, 81, 82, 106, and 107 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "increased to represent 5% of the total amino acid content" is unclear. Amino acids do not represent themselves. Moreover, the claims are better suited to claiming "at least" a certain percentage, since exactly 5% or 10% is

not the intent of the claims. The Examiner suggests the following phrase ---increased to at least 5% of the total amino acid content---.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 57 and 72 are rejected under 35 U.S.C. § 112, first paragraph, new matter, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Methods wherein the interacting proteins are "dimerizing proteins" do not have support in the specification as originally filed. Applicant is required to cancel the new matter in the reply to this Office Action or to cite specific support (page and line number) in the specification.

The Examiner notes that Applicants have noted previously in the prosecution that working examples were provided using dimerizing proteins in the detection of conformational changes on pages 14 and 21. On neither page does the term "dimerizing" appear to the Examiner's knowledge.

18. The previous rejection of Claims 54-83, 97-107, and 115-118 under 35 U.S.C. § 112, first paragraph, as wholly lacking enablement is herein withdrawn. The previous rejection was set forth because the claims were interpreted to include the ability of antibodies (or any interacting

molecule) to assess whether or not the mutated protein had the same conformation as the native protein. While it is clear that no one antibody can completely assess the conformation of a protein, this is not required for the claims to be enabled. The instant claims need only use an antibody that recognizes the native *and* the mutant proteins (if it recognizes native, it must recognize the mutant and to the same extent) as shown by the phrase "confirmed by binding said engineered protein with a set of interacting molecules capable of binding with the native protein" in Claim 54. This view of the claim limitations is broad and evidenced in the art rejections below.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 54-57, 61-62, 64-65, and 117-118 are rejected under 35 U.S.C. § 102(b) as being anticipated by Berkner (USPN 5,288,629). The instant claims are drawn to methods of altering the amino acid composition of a native protein wherein the conformation (structure) of the altered protein is assayed by binding of monoclonal antibodies (ELISA) and wherein the alterations are made at sites determined by homology comparison using mutational analysis (PCR).

Berkner teaches an R152E mutant of human factor VII protein whose recombinant expression levels in BHK cells (baby hamster kidney) are measured by an ELISA using an anti-

Factor VII monoclonal antibody (see columns 11-12). This mutation was (a) performed considering the human and bovine sequences, (b) for the purpose of promoting stability, and (c) using PCR mutagenesis (see Example 1 and Figure 1). This antibody is also used in immunoprecipitations, which indicate that the mutant protein has the conformation of the native (wild-type) protein (see column 12, lines 50-62). Antibodies are inherently dimerizing proteins.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 54-62, 64-66, 68-77, 79-81, 83, 97-102, 104-106, 115-118 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Dyer *et al.* (J. Protein Chemistry (1995) 14(8):665-678) in view of Goldberg (TIBS (1991) 16(10):358-362). The instant claims are drawn to methods of altering the amino acid composition of a native vegetative storage protein wherein the conformation (structure) of the altered protein is assayed by binding of monoclonal antibodies (ELISA), wherein the alterations are made at sites determined by homology comparison using mutational analysis (PCR), and wherein the alteration increase the methionine content to at least 5% of the total amino acid composition.

Dyer *et al.* teach altering the primary structure of phaseolin, a seed storage protein, to enhance the methionine content of the protein to thereby enhance its nutritional value (see

Abstract and page 665). Dyer *et al.* utilize specific knowledge of the protein's structure for determination of the most effective sites for insertion of methionines to cause the least perturbation on the overall structure of the protein; this specific knowledge is a form of secondary structure prediction (see Figure 1). Dyer *et al.* alter the protein using DNA shuffling (see page 668). Dyer *et al.* teach "increasing by tenfold the methionine content from the original 3 to 33 per 397 amino acid residues of the mature phaseolin polypeptide (see page 667, right column). Dyer *et al.* also teach assessing the altered protein's structure using thermal and urea denaturation monitored by circular dichroism (see page 669 and page 673). Dyer *et al.* do not teach assessing the altered protein's structure using monoclonal antibody binding assays.

Goldberg teaches how effective antibodies are in assessing protein conformation, particularly using ELISA assays. Particularly, Goldberg teaches that monoclonal antibodies are good conformational probes useful in assessing protein folding. Moreover, it is well known that antibodies have the ability to dimerize.

It would have been obvious to one of ordinary skill in the art to combine the teachings of Dyer *et al.* and Goldberg to practice methods of altering seed storage proteins wherein antibodies, and not CD spectra, as used to assess protein conformation because in Goldberg and throughout the art, antibodies are known to recognize particular protein conformations specifically. One would have been motivated to practice such methods because antibody binding is easily testable and many antibodies are publicly available for seed storage proteins. One would have had a reasonable expectation of success that antibodies could substitute for CD spectra on the methods of Dyer *et al.*, at least to the extent required by the instant claims, because antibodies are well-known to be capable of recognizing gross protein conformation.

21. Claims 78 and 103 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Dyer *et al.* in view of Goldberg and in view of Arnold *et al.* (Adv. Biochem. Eng. Biotechnol. (1997) 58:1-14). The instant claims are drawn to methods of increasing the nutritional value of a native vegetative storage protein by altering its sequence wherein the conformation (structure) of the altered protein is assayed by binding of monoclonal antibodies and wherein the alterations are made randomly.

Dyer *et al.* teach as described above. Dyer *et al.* do not teach using random mutagenesis methods to produce methionine-enhanced phaseolin.

Goldberg teaches as described above.

Arnold *et al.* teach the use of random point mutagenesis followed by screening for optimizing industrial proteins (see Abstract).

It would have bee obvious to one of ordinary skill in the art to combine the teachings of Dyer *et al.*, Goldberg, and Arnold *et al.* to practice methods of altering seed storage proteins wherein antibodies, and not CD spectra, as used to assess protein conformation after random mutagenesis because in Goldberg and throughout the art, antibodies are known to recognize particular protein conformations specifically and because random mutagenesis is more applicable to the vast majority of seed storage proteins whose homologies and/or secondary structures are less well-known. One would have been motivated to practice such methods because antibody binding is easily testable and many antibodies are publicly available for seed storage proteins and because random mutagenesis is more easily practiced than directed mutagenesis. One would have had a reasonable expectation of success that antibodies could substitute for CD spectra on the methods of Dyer *et al.*, at least to the extent required by the instant claims, because

antibodies are well-known to be capable of recognizing gross protein conformation. One would have had a reasonable expectation of success that random mutagenesis would produce the desired mutants because nutritionally valued amino acids are common (9 out of 20).

Other Art of Record

22. The following are related art not used in rejections above:

a) Falco *et al* (USPN 5,559,223) teaches the production of synthetic seed storage proteins of particular structures, which structures are assayed by circular dichroism (see column 15) and structure-specific antibodies (see column 31). The methods of Falco *et al.* do not utilize a native protein that is modified.

b) Lopes *et al.* (Biotechnol. Nutr. Proc. Int. Symp., 3rd (1992) 237-252) teach engineering of zein proteins in maize to increase their lysine content. The mutant proteins are monitored for their ability to aggregate as a gross measure of conformation.

c) Jaynes JM (Biotechnology in the Feed Industry, Proceedings of Alltech's Annual Symposium, 10th, Lexington, KY, May 1994, 129-153) is a review article.

Conclusion

23. No claims are allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
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KMK
November 12, 2002